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Correlation of C-Reactive Protein (CRP) Levels with D-Dimer Levels in COVID-19 Patients

Churiyyah Eka Choirunisa[1], Retno Martini Widhyasih[1], Rizana Fajrunni'mah[1]
[1]Jurusan Teknologi Laboratorium Medis, Poltekkes Kemenkes Jakarta III, Indonesia
*e-mail: retnomartiniw@gmail.com

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ABSTRACT
Coronavirus disease 2019 is caused by SARS-CoV-2 infection. COVID-19 causes increased levels of proinflammatory cytokines, so CRP and d-dimer levels in COVID-19 patients tend to increase. This study aimed to analyze the correlation between C-Reactive Protein (CRP) levels and D-dimer levels in COVID-19 patients. This research method is analytic observational by using cross-sectional secondary data. The population of this study were all COVID-19 inpatients at Budhi Asih Hospital, East Jakarta, with a sample of 338 patients and were taken by random sampling. The results of this study found that female and male COVID-19 patients had the same risk of being infected with female patients as much as 52,7% and male patients amounting to 47,3%. Most COVID-19 patients occurred at the age of ≥60 years, namely 32,2%. All patients, which is 100% patients had high CRP levels, with a mean of 76,06 mg/L. As for D-dimer levels, 47,9% of patients had normal D-dimer levels and 52,1% had high D-dimer levels with an average of 721,48 ng/mL. The results of the Spearman's correlation test obtained a p value = 0,000, so it can be seen that there is a correlation between C-Reactive Protein (CRP) levels and D-dimer levels in COVID-19 patients with a correlation strength of 0,300 (medium). An increase in CRP levels followed by an increase in D-dimer levels but evaluation of other laboratory examination parameters also needs to be considered.
Keywords*: COVID-19; C-Reactive Protein (CRP); D-dimer*

ABSTRAK
Coronavirus disease 2019 adalah penyakit yang diakibatkan oleh infeksi SARS-CoV-2. COVID-19 menyebabkan meningkatnya kadar sitokin proinflamasi sehingga kadar C-Reactive Protein (CRP) dan D-dimer pada pasien COVID-19 cenderung meningkat. Penelitian ini bertujuan untuk menganalisis korelasi antara kadar CRP dengan kadar D-dimer pada pasien rawat inap COVID-19. Metode penelitian ini adalah obervasional analitik dengan menggunakan data sekunder secara cross sectional. Populasi penelitian ini adalah seluruh pasien rawat inap COVID-19 di RSUD Budhi Asih Jakarta Timur dengan sampel sebanyak 338 pasien yang memiliki catatan hasil pemeriksaan CRP dan D-dimer dan diambil secara random sampling.

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Hasil dari penelitian ini didapatkan bahwa pasien COVID-19 berjenis kelamin perempuan dan laki-laki, memiliki risiko yang sama untuk terinfeksi dengan pasien perempuan sebanyak 52,7% dan pasien laki-laki berjumlah 47,3%. Pasien COVID-19 paling banyak terjadi pada usia ≥60 tahun yaitu 32,2%. Seluruh pasien yaitu 100% memiliki kadar CRP yang tinggi, dengan rata-rata 76,06 mg/L. Sedangkan untuk kadar D-dimer, 47,9% pasien memiliki kadar D-dimer normal dan 52,1% memiliki kadar D-dimer yang tinggi dengan rata-rata 721,48 ng/mL. Hasil Uji korelasi Spearman's didapatkan nilai p = 0,000, sehingga dapat diketahui bahwa terdapat korelasi antara kadar C-Reactive Protein (CRP) dengan kadar D-dimer pada Pasien COVID-19 dengan kekuatan korelasi sedang (r = 0,300). Peningkatan kadar CRP yang diikuti dengan peningkatan kadar D-dimer namun evaluasi terhadap parameter pemeriksaan laboratorium lainnya juga perlu diperhatikan.
Kata Kunci: *COVID-19; C-Reactive Protein (CRP); D-dimer*

INTRODUCTION

Coronavirus disease 2019 or better known as COVID-19 is a disease caused by infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which is a new type of virus discovered from β-coronavirus. The first case of COVID-19 was reported in December 2019 in the city of Wuhan, Hubei Province, China, which then spread to various countries and became a pandemic ((Wilson *et al.*, 2020). COVID-19 has spread to 223 countries with a total of 1,745,880 cases as of 31 December 2021 (World Health Organization, 2021) and on the same day the Indonesian government reported 4,262,720 confirmed cases of COVID-19 with 144,094 of them declared dead (COVID-19 Handling Task Force, 2021).

DKI Jakarta Province as the capital city of Indonesia had 865,297 positive COVID-19 cases as of December 31 2021, making DKI Jakarta one of the provinces with the highest number of COVID-19 cases in Indonesia and particularly East Jakarta the region as the most COVID-19 cases with cases reaching 213,389 ((Dinas Kesehatan DKI Jakarta, 2022a). Referral hospitals for COVID-19 patients in the East Jakarta area, one of which is RSUD Budhi Asih (Dinas Kesehatan DKI Jakarta, 2022b).

The SARS-CoV-2 virus spreads through respiratory droplets with an incubation period of 1-14 days (Wilson *et al.*, 2020). Each patient can show different symptoms, with the most common symptoms that can be experienced are fever, cough, fatigue, and loss of the ability to taste and smell. Apart from that, patients can also experience less common symptoms such as sore throat, headache, pain, diarrhea, skin rashes and eye irritation (WHO, 2022). Patients with higher degrees of disease can show severe clinical manifestations such as severe pneumonia,

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sepsis, septic shock, acute respiratory distress syndrome (ARDS), and multiple organ dysfunction syndrome (MODS) (Wilson *et al.*, 2020).

With symptoms that have been recognized, examination parameters are needed that can have good diagnostic accuracy in confirming COVID-19. The gold standard for COVID-19 diagnostics is Quantitative Reverse Transcription Polymerase Chain Reaction (qRT-PCR) which is a type of Nucleic Acid Amplification Test (NAAT) method (Indonesian Ministry of Health, 2021). In addition, supporting examinations are required such as physical examination, routine hematology and chemistry tests, computed tomography (CT), and serology for COVID-19 immunoglobulin (Carpenter *et al*., 2020). Laboratory supporting examinations are needed because the virus can damage the vital organs of the heart, liver and kidneys and the main examinations used are complete blood count, coagulation and fibrinolysis tests, and parameters for inflammation examination (Pourbagheri-sigaroodi, 2020).

The SARS-CoV-2 virus attacks the human respiratory tract, especially the cells lining the alveoli. The virus has a glycoprotein in the enveloped spike (Protein S) which then binds to the ACE 2 receptor on the plasma membrane of human cells to infect. The virus will replicate the required genetic material and proteins and form new virions on the cell surface (Levani, Prastya and Mawaddatunnadila, 2021).

When the virus enters the cell, the viral antigen will be presented to the Antigen Presentation Cell (APC) which then T cells and B cells will mediate the immune and cellular system response. The humoral immune system will produce IgM and IgG, but viruses can evade the immune system by inducing double membrane vesicles that do not have pattern recognition receptors (PRRs) and replicating in these vesicles (Levani, Prastya and Mawaddatunnadila, 2021). Proinflammatory mediators such as interleukin 6 (IL-6) and IL-1β also increase and produce CRP in response (McFadyen *et al*., 2018). Evaluation of C-reactive protein (CRP) levels is routinely used to assess inflammatory markers, the levels of which will then increase in most COVID-19 patients, and can indicate the severity of the disease (Luo *et al*., 2020). CRP was chosen to evaluate inflammation because it is cheap and easy to perform with very specific results (Zadeh *et al*., 2018) and has superior diagnostic value compared to procalcitonin (Pourbagheri-sigaroodi, 2020), and can

differentiate well between severe and non-severe pneumonia in COVID-19 (Vita and Syambani, 2020).

As a result of the increase in pro-inflammatory mediators that occur, it will cause lung organ damage with the formation of fibrotic tissue (Levani, Prastya and Mawaddatunnadila, 2021). The tissue is broken down into soluble fragments (D-dimers) formed from enhanced fibrin synthesis activating plasminogen and plasmin (Grobler *et al*., 2020). D-dimer examination, which is a fibrin degradation product, was used because it has proven useful in clinical decision rules for pulmonary embolism (Yu *et al*., 2020). Potential mechanisms of increased D-dimer levels in patients with COVID-19 are pulmonary endothelial injury with inflammation-related intra-alveolar fibrin deposits as well as systemic endothelial injury with diffuse thrombosis of smaller vessels (Valerio *et al*., 2021). Elevated D-dimer may effectively contribute to reflect disease progression towards an unfavorable clinical picture (Pourbagheri-sigaroodi, 2020).

In research by Yu *et al* (2020), it was found that increasing D-dimer levels was related to inflammatory markers, namely CRP. Research by Valerio *et al* (2021) shows that increased levels of D-dimer and CRP occur in COVID patients with a high level of severity so that these parameters can help monitor disease activity (Valerio *et al*., 2021). In research conducted in Indonesia by Wardika and Sikersa (2021), it was also found that CRP and D-dimer levels showed a significant relationship with the severity of infection and mortality. However, there has been no research on the correlation between CRP levels and D-dimer levels in COVID-19 patients conducted at Budhi Asih Regional Hospital with data from the first examination after the patient was confirmed positive for SARS-CoV-2 and was treated at the hospital.

Based on the description above, the author wants to analyze the correlation between C-Reactive Protein (CRP) levels and D-dimer levels in COVID-19 patients.

METHOD

This research has received permission from the research ethics commission of the Budhi Asih Jakarta Regional General Hospital with ethics letter number No. 50/KEP-ETIK/III/2022 dated March 18 2022. This research is observational analytic with a cross sectional design.

This research, which was conducted at the Budhi Asih Regional General Hospital in January - June 2022, used all data on 1319 COVID-19 inpatients in 2021 at the Budhi

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Asih Regional General Hospital as the population and 338 patients were selected as samples by random sampling. The samples used were patients who had odd medical record numbers.

The research procedure begins with submitting a letter of application for an ethical review and research permit to the Poltekkes institution, Ministry of Health, Jakarta III, then the application letter along with the other requirements were handed over to the Budhi Asih Regional Hospital. After the ethics letter and permission letter for data collection have been processed, the medical record data containing CRP and D-dimer data is sorted, with the examination result data is recorded, recapitulated, and is presented in the form of tables and narratives.

Data were analyzed univariately to describe the results of examination of CRP and D-dimer levels in COVID-19 patients at Budhi Asih Regional Hospital in the form of mean, median, standard deviation, minimum value, and maximum value. Bivariate analysis using statistical software for Windows were also carried out using Kolmogorf-Smirnov for data normality distribution and continued with Spearman test because the data is not normally distributed.

RESULTS AND DISCUSSION

Table 1 Frequency distribution of COVID-19 patients based on gender and age at Budhi Asih Regional Hospital in 2021

Variable	Frequency (n)	Percentage (%)
Gender		
Man	160	47,3
Woman	178	52,7
Total	**338**	**100**
Age (Years)		
≤5	1	0,3
6-19	7	2,1
20-29	25	7,4
30-39	42	12,4
40-49	66	19,5
50-59	88	26
≥60	109	32,2
Total	**338**	**100**

Age categorized based on DKI Jakarta Health Service (https://corona.jakarta.go.id/id/terminologi-lama)

The characteristics of COVID-19 patients can be seen in Table 1 and it is known that the characteristics based on gender consist of 178 people (52.7%) female and 160 male

patients (47.3%). This is in line with data from the DKI Jakarta Health Service (2022) which shows that almost equal proportions of confirmed cases of COVID-19 are 51.04% female and 48.96% male. In Satria, Kuncioho and Chalidyanto's (2020) research, results were also obtained with balanced proportions, namely from 253 data, 50.2% of whom were women. A fairly balanced proportion can also be seen in the research of Maryati *et al*. (2022), namely 55.9% of COVID-19 experienced by men with a total of 501 data. This research also shows that COVID-19 most often occurs in people aged ≥60 years, namely 109 patients (32.2%), followed by with ages 50-59 years, namely 88 patients (26%). This is in line with research conducted by Nanda Nur Illah (2021) which states that the risk of being infected with a virus will increase when a person reaches the age of 40 because a person's immunity tends to decrease so that their susceptibility to pathogens becomes higher. Apart from that, those aged 45-60 years have a high level of productivity and mobility (Nanda Nur Illah, 2021). These results are also reinforced by research conducted by Biswas *et al*. (2021) which explains that someone over 50 years of age has a higher risk of exposure to the virus and death than those under age, which is related to higher ACE2 gene expression in older patients (Biswas *et al*., 2021).

Table 2. Descriptive analysis of CRP and D-dimer examination results in patients COVID-19 at Budhi Asih Regional Hospital in 2021

Variable	SD	Mean	Median	Max.	Min.
CRP	65,615	76,06	60,50	200	5
D-dimer	573,397	721,48	538,50	2000	100

Table 2 Frequency distribution of COVID-19 patients based on CRP levels and D-dimer levels at Budhi Asih Regional Hospital in 2021

Variable	Frequency (n)	Percentage (%)
CRP levels		
High (≥5 mg/L)	338	100
Total	**338**	**100**
D-dimer levels		
High (<500 ng/mL)	162	47,9
Increased (≥500 ng/mL)	176	52,1
Total	**338**	**100**

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Based on Table 3, all subjects from this study, namely 338 patients (100%) experienced an increase in CRP levels with a mean of 76.06 mg/L with a range of 5-200 mg/L which can be seen in Table 2. These results are in line with the theory that the SARS-CoV-2 virus can induce CRP production which is mediated by increased Angiotensin II activity, this plays a role in the severity of COVID-19 (Mosquera-Sulbaran *et al.*, 2021). This theory is also strengthened by research from Chen *et al.* (2020) which shows that there is a positive relationship between CRP levels and the severity of COVID-19 and the duration of hospitalization, and research by Zhang *et al.* (2020) explains that the most common laboratory findings for COVID-19 patients is an increase in CRP levels (Zhang *et al.*, 2020). Meanwhile, in the D-dimer level variable, 162 patients (47.9%) had normal levels and the other 176 patients (52.1%) experienced an increase with a mean of 721.48 ng/mL with a level range of 100-2000 ng/mL. This is in line with research conducted by Shi *et al.* (2020) which shows that coagulopathy that occurs in patients shows increased levels of D-dimer as well as research by Zhou *et al.* (2020) which states that there are COVID-19 patients with increased levels of D-dimer and some have not increased. After attachment of the SARS-CoV-2 virus then ACE2 dysregulation will occur and then angiotensin II regulation will increase and induce plasminogen activator inhibitor-1 (PAI-1) which is a suppressor of fibrinolysis and may also explain the fibrin deposits seen in the lung alveoli (Manzoor *et al.*, 2021) . Due to the high fibrinolytic capacity of the lungs, vigorous fibrinolysis occurs which causes the production of D-dimer in the bloodstream (Samprathi and Jayashree, 2021).

Table 3 Cross tabulation of CRP and D-dimer examination results in patients COVID-19 at Budhi Asih Regional Hospital in 2021

Variable	D-dimer levels		Total
	Normal	Increased	
Increased CRP levels	162	176	338
Total	**162**	**176**	**336**

Table 4 shows that there were 162 COVID-19 patients who experienced increased CRP levels but had normal D-dimer levels, while 176 patients experienced increased CRP levels followed by increased D-dimer levels. This is in line with the results of research by Ullah *et al.* (2020) which explains that increasing D-dimer levels is a more sensitive

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marker of severity, so that increasing CRP levels followed by increasing D-dimer levels will result in high disease severity as well as in research Zhu *et al*. (2020) stated that the majority of patients with high and critical severity experienced increased CRP levels and D-dimer levels.

Patients who have high CRP levels but normal D-dimer levels can occur because the data used is data from the first examination (screening) after the patient was confirmed positive for SARS-CoV-2, besides that CRP, which is an acute phase protein, can increase first before coagulation occurs. inside the body. Meanwhile, patients who have both high CRP and D-dimer levels can experience hyperinflammation triggered by chronic inflammatory comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (smokers), coronary heart disease, kidney failure, as well as autoimmunity and age continued (Sumantri, 2022). In research data, it is known that COVID-19 often occurs at ages ≥ 60 and patients are at very high risk of having comorbid diseases that cause hyperinflammation, so in this study the results showed high CRP levels followed by high D-dimer levels.

Table 4 Data Normality Test

Variable	p value
CRP levels	0.000
D-dimer levels	0.000

The results of the data normality test using the Kolmogorov-Smirnov test showed that CRP levels and D-dimer levels had a p-value = 0.000 ($p<0.05$). It can be concluded that both data have a non-normal distribution, so the Spearman test is used for correlation test.

Table 5 Correlation of CRP Levels with D-dimer Levels

Variable	Value		
	N	p	Rho
CRP levels D-dimer levels	338	0.000	0.300

The Spearman correlation test in Table 6 revealed p = 0.000 so there is a correlation between C-Reactive Protein (CRP) levels with D-dimer levels in COVID-19 patients with moderate correlation strength (r = 0.300). In this study, moderate correlation

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results were obtained with a positive test direction, meaning if there is an increase in CRP levels it can be followed by an increase in D-dimer, but not in every case of COVID-19 patients. The results of this study are in line with the results of research conducted by Yu *et al.* (2020), namely that there is a moderate correlation between CRP levels and D-dimer levels ($r = 0.426$, $P < 0.05$) and in research conducted by Wati *et al*. (2021) also showed moderate correlation results in a positive direction towards CRP and D-dimer levels in COVID-19 patients ($r = 0.517$; $p = 0.000$).

CONCLUSION

Research conducted at the Budhi Asih Regional General Hospital with data on 338 COVID-19 patients for the period January – December 2021 concluded that COVID-19 dominantly occurred in women (52.7%) at vulnerable ages of ≥60 years (32.2%). Meanwhile, all patients revealed an increase in CRP levels in comparison with D-dimer levels which were varied (176 patients of high-level group and 162 patients of normal group). Analysis of both CRP and D-dimer indicated that there is a correlation between CRP levels and D-dimer levels ($P = 0.000$) with a positive direction and moderate strength ($r = 0.300$), meaning high CRP levels can be followed by high D-dimer levels, age and comorbid diseases can be factors in the high levels of both that. Nevertheless, evaluation of other laboratory examination parameters also needs to be considered.

High levels of CRP followed by high levels of D-dimer can reflect inflammation caused by SARS-CoV-2 virus infection and is followed by coagulopathy which will impact organ damage and severity in COVID-19 patients. Although this does not happen in all cases, these CRP and D-dimer examination parameters can be a prognosis and marker of organ damage and severity in COVID-19 patients by continuing to evaluate other laboratory examination parameters so that health workers can provide appropriate treatment to patients.

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REFERENCES

Athena, A., Laelasari, E. and Puspita, T. (2020) 'Implementation of

Disinfection in Preventing Covid-19 Transmission and Potential Risks to Health in Indonesia', Journal of Health Ecology, 19(1), pp. 1–20. doi: 10.22435/jek.v19i1.3146.

Benziger, CP et al. (2021) 'The Telehealth Ten: A Guide for a Patient-Assisted Virtual Physical Examination', American Journal of Medicine, 134(1), pp. 48–51. doi: 10.1016/j.amjmed.2020.06.015.

Berhandus, C., Ongkowijaya, JA and Pandelaki, K. (2021) 'Relationship of Vitamin D Levels and C-Reactive Protein Levels with Clinical 2019 Coronavirus Disease Patients', e-CliniC, 9(2), pp. 370–378. doi: 10.35790/ecl.9.2.2021.33043.

Chang, M.C., Hur, J. and Park, D. (2020) 'Interpreting the COVID-19 Test Results: A Guide for Physiatrists', American Journal of Physical Medicine and Rehabilitation, 99(7), pp. 583–585. doi: 10.1097/PHM.0000000000001471.

Chen, W. et al. (2020) 'Plasma CRP levels are positively associated with the severity of COVID-19', Annals of Clinical Microbiology and Antimicrobials, 19, pp. 1–7. doi: 10.1186/s12941-020-00362-2.

COVID-19 Handling Task Force (2021) COVID-19 Distribution Map, committee for handling COVID-19 and National Economic Recovery. Available at: https://covid19.go.id/peta-sebaran-covid19 (Accessed: 7 April 2021).

Dashraath, P. et al. (2020) 'Coronavirus disease 2019 (COVID-19) pandemic and pregnancy', American Journal of Obstetrics and Gynecology, 222(6), pp. 521–531. doi: 10.1016/j.ajog.2020.03.021.

DKI Jakarta Health Service (2021) 'Village-Based COVID-19 Statistical Information', https://corona.jakarta.go.id/. Available at: https://corona.jakarta.go.id/id/statistik-covid-19-berbasis-kelurahan (Accessed: 31 December 2021).

DKI Jakarta Health Service (2022) 'List of Referral Hospitals', https://corona.jakarta.go.id/. Available at: https://corona.jakarta.go.id/id/contact (Accessed: 7 February 2022).

DKI Jakarta Health Service (2022) 'Monitoring Data', https://corona.jakarta.go.id/. Available at: https://corona.jakarta.go.id/en/data-pemantauan (Accessed: 10 February 2022).

DKI Jakarta Health Service (2022) 'Old Terminology Data', https://corona.jakarta.go.id/. Available at: https://corona.jakarta.go.id/id/terminologi-lama (Accessed: 12 June 2022).

DxGen (2020) 'Multi-marker Point-of-care Testing System EPHITOD®616', pp. 1–26.

EDAN Diagnostics (2020) Product Catalogue, Edan Instruments. Available at: https://www.edan.com/Uploads/20201027035530_187173.pdf (Accessed: 28 December 2021).

Gonçalves, FAR et al. (2021) 'Use and misuse of biomarkers and the role of D-dimer and C-reactive protein in the management of COVID-19: A post-hoc analysis of a prospective cohort study', Clinics (Sao Paulo, Brazil), 76 (1), p. e3547. doi: 10.6061/clinics/2021/e3547.

Hao, W. et al. (2021) 'Binding of the SARS-CoV-2 spike protein to glycans', Science Bulletin, 2019. doi: 10.1016/j.scib.2021.01.010.

Kahar, F. et al. (2020) 'The Epidemiology of COVID-19, Attitudes and Behaviors of the Community During the Covid Pandemic in Indonesia', International Journal of Innovative Science and Research Technology, 5(8), pp. 1681–1687. doi: 10.38124/ijisrt20aug670.

Kalma, K. (2018) 'Study of C-Reactive Protein (Crp) Levels in Type 2 Diabetes Mellitus Patients', Health Analyst Media Journal, 1(1). doi: 10.32382/mak.v1i1.222.

Indonesian Ministry of Health (2021) 'Decree of the Minister of Health of the Republic of Indonesia number hk.01.07/menkes/4642/2021 concerning the implementation of examination laboratories', 2019, pp. 1–69.

Kumar, S. et al. (2019) 'Morphology, Genome Organization, Replication, and Pathogenesis of Severe Acute Respiratory Syndrome Coronavirus 2', 2, pp. 23–31.

Lazuardi, BP (2018) Relationship between the severity of dengue infection and ALT and C-Reactive Protein levels in pediatric patients at Saiful Anwar Hospital, Malang. Brawijaya University.

Levani, Prastya and Mawaddatunnadila (2021) 'Coronavirus Disease 2019 (COVID-19): Pathogenesis, Clinical Manifestations and Therapeutic Options', Journal of Medicine and Health, 17(1), pp. 44–57. Available at: https://jurnal.umj.ac.id/index.php/JKK/article/view/6340.

Long, C. et al. (2020) 'Diagnosis of the Coronavirus disease (COVID-19): rRT-PCR or CT?', European Journal of Radiology, 126(March), p. 108961. doi: 10.1016/j.ejrad.2020.108961.

Luo, X. et al. (2020) 'Prognostic Value of C-Reactive Protein in Patients with Coronavirus 2019', Clinical Infectious Diseases, 71(16), pp. 2174–2179. doi: 10.1093/cid/ciaa641.

Manzoor, D. et al. (2021) 'Improvement in plasma D-dimer levels in severe SARS-CoV-2 infection can be an indicator of fi brinolysis suppression', 0(March).

Maryati, W. et al. (2022) 'Characteristic Analysis of Inpatients with Covid-19 Cases', Infokes: Scientific Journal of Medical Records and Health Informatics, 12(1), pp. 20–25. doi: 10.47701/infokes.v12i1.1354.

McFadyen, J.D. et al. (2018) 'Dissociation of C-reactive protein localizes and amplifies inflammation: Evidence for a direct biological role of C-reactive protein and its conformational changes', Frontiers in Immunology, 9(JUN). doi: 10.3389/fimmu.2018.01351.

Mosquera-Sulbaran, JA et al. (2021) 'C-reactive protein as an effector molecule in Covid-19 pathogenesis', Reviews in Medical Virology, 31(6). doi: 10.1002/rmv.2221.

Nanda Nur Illah, M. (2021) 'Analysis of the Influence of Comorbidities, Age and Gender on Increasing Death Rates during the Covid-19 Pandemic', Journal of Social Science, 1(10), pp. 1228–1233. doi: 10.36418/sosains.v1i10.232.

Paez, D. et al. (2020) 'COVID-19 pandemic: guidance for nuclear medicine departments', European Journal of

Nuclear Medicine and Molecular Imaging, 47(7), pp. 1615–1619. doi: 10.1007/s00259-020-04825-8.

Park, WB et al. (2020) 'Virus Isolation from the First Patient with SARS-CoV-2 in Korea', J Korean Med Sci, 7. doi: https://doi.org/10.3346/jkms.2020.35.e84.

Pathak, A. and Agrawal, A. (2019) 'Evolution of C-reactive protein', Frontiers in Immunology, 10(APR). doi: 10.3389/fimmu.2019.00943.

Pourbagheri-sigaroodi, A. (2020) 'Since January 2020 Elsevier has created a COVID-19 resource center with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource center is hosted on Elsevier Connect , the company's public news and information', Clinica Chimica Acta 510, (January).

Riley, R. S. et al. (2016) 'Widely used types and clinical applications of D-dimer assay', Lab Medicine, 47(2), pp. 90–102. doi: 10.1093/labmed/lmw001.

Romagnoli, S., Peris, A. and Gaudio, AR De (2020) 'SARS-CoV-2 and COVID-19 : from the bench to the bedside', Physiological Reviews.

Samprathi, M. and Jayashree, M. (2021) 'Biomarkers in COVID-19: An Up-To-Date Review', Frontiers in Pediatrics, 8(December 2019), pp. 1–12. doi: 10.3389/fped.2020.607647.

Satria, Tutupoho, and Chalidyanto. (2020) 'Analysis of Risk Factors for Death with Covid-19 Comorbid Disease', Silampari Nursing Journal, 4(1), pp. 1689–1699.

COVID-19 Handling Task Force (2021) COVID-19 Distribution Map, committee for handling COVID-19 and National Economic Recovery. Available at: https://covid19.go.id/peta-sebaran-covid19 (Accessed: 7 April 2021).

Shah, S. et al. (2020) 'Elevated d -dimer levels are associated with increased risk of mortality in coronavirus disease 2019: A systematic review and meta-analysis', Cardiology in Review, 28(6), pp. 295–302. doi: 10.1097/CRD.0000000000000330.

Sheikhi, K., Shirzadfar, H. and Sheikhi, M. (2020) 'A Review on Novel Coronavirus (Covid-19): Symptoms, Transmission and Diagnosis Tests Research in Infectious Diseases and Tropical Medicine A Review on Novel Coronavirus (Covid- 19): Symptoms , Transmission and Diagnostic Tests', Research in Infectious Diseases and Tropical Medicine, 2(1), pp. 1–8.

Sheriff, A. et al. (2021) 'C-Reactive Protein Triggers Cell Death in Ischemic Cells', Frontiers in Immunology, 12(February), pp. 1–8. doi: 10.3389/fimmu.2021.630430.

Shi, C. et al. (2020) 'The Potential of Low Molecular Weight Heparin to Mitigate Cytokine Storm in Severe COVID-19 Patients: A Retrospective Cohort Study', Clinical and Translational Science, 13(6), pp. 1087–1095. doi: 10.1111/cts.12880.

Sproston, NR and Ashworth, JJ (2018) 'Role of C-reactive protein at sites of inflammation and infection', Frontiers in Immunology, 9(APR), pp. 1–11. doi: 10.3389/fimmu.2018.00754.

Sumantri, S. (2022) Getting to Know Cytokine Storms, Causes of Organ Damage in COVID-19 Patients, www.siloamhospitals.com. Available

at: https://www.siloamhospitals.com/information-siloam/article/mengenal-badai-sitokin-besar-kekerasan-organ-pada-patient-covid-19 (Accessed: 19 July 2022).

Sun, J. et al. (2020) 'COVID-19: Epidemiology, Evolution, and Cross-Disciplinary Perspectives', Trends in Molecular Medicine, 26(5), pp. 483–495. doi: 10.1016/j.molmed.2020.02.008.

Ullah, W. et al. (2020) 'Predictability of CRP and D-Dimer levels for in-hospital outcomes and mortality of COVID-19 ABSTRACT', Journal of Community Hospital Internal Medicine Perspectives, 10(5), pp. 402–408. doi: 10.1080/20009666.2020.1798141.

Valerio, L. et al. (2021) 'Course of D-Dimer and C-Reactive Protein Levels in Survivors and Nonsurvivors with COVID-19 Pneumonia: A Retrospective Analysis of 577 Patients', Thrombosis and Haemostasis, 121(1), pp. 98–101. doi: 10.1055/s-0040-1721317.

Velavan, TP and Meyer, CG (2020) 'The COVID-19 epidemic', Tropical Medicine and International Health, 25(3), pp. 278–280. doi: 10.1111/tmi.13383.

Vita, G. and Syambani, Z. (2020) 'Since January 2020 Elsevier has created a COVID-19 resource center with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource center is hosted on Elsevier Connect , the company 's public news and information', Med Clin (Barc), (January), pp. 143–151.

Wati, L. et al. (2021) 'C-Reactive Protein Correlates with D-Dimer Levels', 5(1), pp. 1–9.

Weitz, JI, Fredenburgh, JC and Eikelboom, JW (2017) 'A Test in Context: D-Dimer', Journal of the American College of Cardiology, 70(19), pp. 2411–2420. doi: 10.1016/j.jacc.2017.09.024.

WHO (2020) 'Diagnostic tests for SARS-CoV-2', Interim Guidance, pp. 1–19.

WHO (2022) Coronavirus disease (COVID-19), https://www.who.int/health-topics. Available at: https://www.who.int/health-topics/coronavirus#tab=tab_3 (Accessed: 16 May 2022).

William et al. (2020) 'Coagulopathy in Coronavirus Disease -2019 (COVID-19): Literature review', Medical Science Digest, 11(3), pp. 749–756. doi: 10.15562/ism.v11i3.766.

World Health Organization (2021) About us : World Health Organization, WHO. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (Accessed: 6 April 2021).

Yang, C. et al. (2021) 'Myocardial injury and risk factors for mortality in patients with COVID-19 pneumonia', International Journal of Cardiology, 326, pp. 230–236. doi: 10.1016/j.ijcard.2020.09.048.

Yang, Y. et al. (2020) 'SARS-CoV-2: characteristics and current advances in research', Virology Journal, 17(1), pp. 1–17. doi: 10.1186/s12985-020-01369-z.

Yu, B. *et al.* (2020) "Evaluation of variation in D-dimer levels among COVID-19 and bacterial pneumonia: a retrospective analysis," *Journal of Thrombosis and Thrombolysis*, 50(3), hal. 548–557. doi: 10.1007/s11239-020-02171-y.

Zadeh, M.T. et al. (2018) 'Diagnostic Value of Hematologic and Inflammatory Profile in Adjunction to Blood Culture in Patients Suspected of Septicemia', International Journal of Pediatrics-Mashhad, 6(1), pp. 6903–6910. doi: 10.22038/ijp.2017.23837.2015.

Zhang, Z. L. *et al.* (2020) "Laboratory findings of COVID-19: a systematic review and meta-analysis," *Scandinavian Journal of Clinical and Laboratory Investigation*, 80(6), hal. 441–447. doi: 10.1080/00365513.2020.1768587.

Zhou, F. *et al.* (2020) "Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study," *The Lancet*, 395(10229), hal. 1054–1062. doi: 10.1016/S0140-6736(20)30566-3.

Zhu, J. *et al.* (2020) "Correlations of ct scan with high-sensitivity c-reactive protein and d-dimer in patients with coronavirus disease 2019," *Pakistan Journal of Medical Sciences*, 36(6), hal. 1391–1401. doi: 10.12669/PJMS.36.6.2961.

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